

[REVIEW ARTICLE]

Clinical and Genetic Aspects of Behçet's Disease in Japan

Yohei Kirino and Hideaki Nakajima

Abstract:

Patients with Behçet's disease (BD) suffer from episodic ocular and mucocutaneous attacks, resulting in a reduced quality of life. The phenotype of Japanese BD has been changing over the past 20 years, and the rate of human leukocyte antigen (*HLA*)-*B*51*-positive complete type is decreasing while that of intestinal type is increasing. This phenotypical evolution may be related to changes in as-yet-unknown environmental factors, as the immigration influx in Japan is low. Mechanisms discovered by genome-wide association studies include *ERAP1*-mediated HLA class I antigen bounding pathway, autoinflammation, Th17 cells, natural killer cells, and polarized macrophages, a similar genetic architecture to Crohn's disease, ankylosing spondylitis, and psoriasis. As for treatments, management guidelines have been implemented, and the development of tumor necrosis factor (TNF) inhibitors is markedly improving the outcome of BD, but evidence supporting treatment for special-type BD is limited. The classification of BD into distinct clusters based on clinical manifestations and genetic factors is crucial to the development of optimized medicine.

Key words: Behçet's disease, genetics, environmental factors, GWAS, HLA, *ERAP1*

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Introduction

Behçet's disease (BD), initially reported by Turkish dermatologist Hulusi Behçet in 1937, is a disease of unknown cause, characterized by episodic inflammation of multiple organs, such as the eyes, skin, mucosa, brain, intestine, and large vessels (1, 2). A diagnosis of BD is made by a combination of clinical manifestations, and there is no disease-specific symptom or laboratory test for diagnosing the disease. BD can be one of the toughest rheumatic diseases to diagnose owing to its heterogeneity and "time and space" development of lesions.

The diagnosis of BD has become even more challenging in recent years in Japan; the rate of incomplete BD is increasing (3), and their phenotypes are becoming milder (4). For example, BD was the most frequent cause of non-infectious uveitis in Japan until the 1980s, but currently, sarcoidosis is the most frequent cause (5). Such BD patients who may not meet the BD diagnostic criteria can still develop severe organ damage, such as intestinal BD, and thus the identification of the characteristics and prognosis of modern-day BD patients is warranted.

In this review, we describe the recent epidemiological and genetic data of BD, management guidelines and suggest a treatment strategy to cope with issues in BD faced today.

The Diagnosis of BD

BD is a heterogeneous disease with multiple-organ involvement. Fig. 1 shows the variety of symptoms found in BD patients. As such, the condition is also called Behçet syndrome (1). In Japan, the diagnostic criteria of Behçet's Disease Research Committee were revised in 1987, and the Ministry of Health, Labor and Welfare of Japan has since been using these criteria to diagnose the disease (Table 1) (6).

The diagnosis of BD is made based on a combination of symptoms; recurrent aphthous oral ulcers, skin lesions, ocular inflammation, and genital ulcers are included as "major symptoms," and patients with all four major symptoms during the clinical course are defined as having complete-type BD. Arthritis, intestinal ulcers, epididymitis, vascular lesions, and neurological disease are considered "minor symptoms." The confirmation of the recurrence of these conditions is crucial to establish the diagnosis of BD. Patients

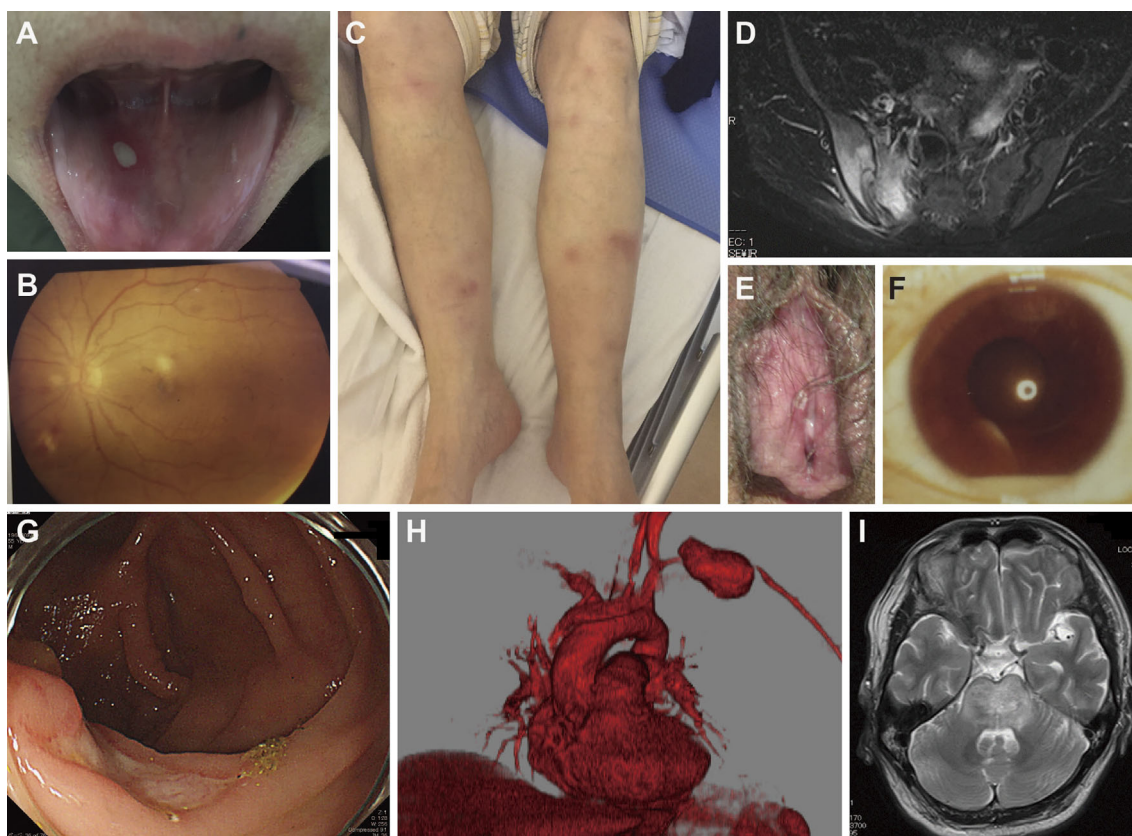


Figure 1. Clinical manifestations in Japanese patients with Behçet's disease. Various BD symptoms found in Japanese BD patients. A: oral ulcer; B: posterior ocular uveitis; C: erythema nodosum; D: MRI T2-weighted image showing right sacroiliitis; E: genital ulcer; F: anterior uveitis with hypopyon; G: deep ulcer in the ileocecum; H: aneurysm of the left subclavian artery; I: MRI T2-weighted image showing acute-type neuro Behçet's disease in the brain stem.

with central nervous system involvement, vascular, and gastrointestinal involvement are categorized as having “special-type” BD. Usually, patients do not present all of the BD symptoms at the same time, and many of the symptoms may appear separately (4). For example, oral ulcers appear an average of seven years before the diagnosis, while special-type BD tends to develop a couple of years after the BD diagnosis (4). Inflammation in the genital and ileocecal areas as well as the brain stem suggest high odds of having BD (1). The phenotype of BD is complicated, as each component of the criteria can further be divided into distinct phenotypes; eye disease can either be anterior or posterior uveitis; skin rash can be pustulosis, erythema nodosum, or superficial venous thrombosis; vascular disease can be an aneurysm or embolism, and so on.

In countries such as Turkey, the International Study Group (ISG) criteria have been used to classify BD (Table 1) (7). The ISG criteria are more stringent than the Japanese criteria, as they do not account for special-type, and the presence of oral ulceration is mandatory. A pathergy test, which is rarely positive in Japanese BD, is included (8). The recently proposed International Criteria for Behçet's Disease (ICBD) account for neuro and vascular BD but not intestinal BD (9). The main reason intestinal BD is not included in

the ISG or ICBD criteria is that intestinal BD is rare in the Middle East (prevalence: about 1-7%), while it is common in Japan (about 12%) (3, 10).

Other symptoms, such as general fatigue, myalgia, chest pain and psychiatric symptoms, are common in BD but are not included in the criteria. In rare cases (at least in Japan), familial Mediterranean fever, spondyloarthritis (SpA; enthesitis and sacroiliitis), MAGIC syndrome (a complication with relapsing polychondritis), IgA nephritis, and myelodysplastic syndrome with trisomy 8 may coexist with BD (11-14). BD is classified as an autoinflammatory disease because of its episodic inflammatory attacks, low prevalence of auto-antibodies, and effectiveness of colchicine (15).

There are no specific laboratory data indicating BD. The serum CRP is lower than that with rheumatoid arthritis (RA), and the interleukin (IL)-6 levels in spinal fluid may be useful for the diagnosis of chronic progressive type neuro-BD (16). Serum IgD has long been measured in Japan, but the clinical relevance of its measurement is uncertain.

Table 1. A Comparison of the Behçet's Disease Criteria.

	Japanese	ISG ⁷	ICBD ⁹
Oral ulcer	◎	●	○ 2 points
Genital ulcer	◎	○	○ 2 points
Skin region	◎	○	○ 1 point
Uveitis	◎	○	○ 2 points
Pathergy test	×	○	○ 1 point
Arthritis	○	×	×
Epididymitis	○	×	×
Gastrointestinal	○	×	×
Neuro	○	×	○ 1 point
Vascular	○	×	○ 1 point

◎ : indicates symptoms included in major criteria, ○ : indicates symptoms included in each set of criteria, × : indicates symptoms not included, ● : indicates that the symptom must be included.

Japanese: 3 major criteria, or uveitis and 1 major or 2 minor criteria, or 2 major and 2 minor criteria are required for the diagnosis; ISG: International Study Group Criteria, 3 out of 5 components are required; ICBD: International Criteria for Behçet's Disease, ≥4 points are required to fulfil the criteria.

Epidemiology and Environmental Factors in BD

BD patients are highly prevalent along the Silk Road (17). In Turkey, the prevalence of BD is 370 per 100,000 people (about 0.4%), but its incidence in Europe and North America is low (1). The prevalence rate in Japan is about 16 per 100,000 people, and 20,035 persons are medical beneficiaries according to the Ministry of Health, Labor and Welfare (2014). There is no marked gender difference in the overall disease, but arthritis and genital ulcer are more common in women, whereas central nervous system and eye lesions are more prevalent in men (3). A possible explanation for the male predominance of neuro-BD is that cigarettes may trigger neuroinflammation and that men tend to smoke more than women (18).

It has long been suggested that both environmental and genetic factors are crucial for the occurrence of BD. Several pieces of circumstantial evidence support the role of environment factors in BD. First, the BD incidence rate of Hawaiians of Japanese descent is reported to be lower than in Japanese patients living in Japan (19). Second, it is well known that the disease ameliorates over time (20). Third, dental treatment and inoculation with *Streptococcus* for vaccination may trigger the BD onset (21). Finally, the phenotype of BD is changing in Japan and Korea, as the proportion of complete-type patients has decreased while that of intestinal-type has increased (3, 22). These data suggest that environmental factors are essential in the etiology of BD. Whenever possible, avoiding skin damage, such as surgical intervention, acupuncture, and moxibustion, which can provoke BD skin reactions, may be recommended.

Genetics of BD

BD is classified as a multigenic disease, and the penetration of individual loci is small. Human leukocyte antigen (*HLA*)-*B*51*, which was reported by Ohno et al. in 1973, confers the strongest genetic predisposition toward BD, as has been shown worldwide, but about 15% of healthy Japanese individuals possess *HLA-B*51*, and about 30% of BD patients do not possess *HLA-B*51* (20, 21). Thus, it is not very useful for the diagnosis of BD (23, 24). However, *HLA-B*51* positivity is associated with uveitis and neuro-BD (25).

We and others have also reported 17 BD disease susceptibility loci, including *HLA-A*26* (*A*03* in Turkish), *IL23R*, *STAT4*, and *ERAP1*, through genome-wide association analyses (GWASs) (Table 2) (26-29). Both HLA-Class I, *ERAP1* and *IL23R* have also been determined to be susceptibility genes of ankylosing spondylitis (AS) and psoriasis, indicating that the pathogenesis of these diseases is similar to that of BD. Fig. 2 depicts the genetic overlap between BD and other SpAs [a disease concept encompassing AS, psoriasis, and inflammatory bowel diseases (IBDs) proposed by Moll et al. (30)]. Recently, the disease concept of "MHC Class I-o-pathy," diseases, which exhibit HLA-class I and *ERAP1* interaction, was proposed (31).

Treatments for BD

Unlike RA, no treat-to-target approach has been developed for BD treatments. In addition, there are only a few disease activity scoring systems available for BD (32, 33). For non-organ damaging symptoms, topical steroid, colchicine, low-dose prednisolone, orally administered non-steroidal anti-inflammatory drugs (NSAIDs) are generally used. High-dose steroids, immunosuppressants such as cyclosporine A, azathioprine (AZA), methotrexate, and anti-tumor necrosis factor (TNF)- α antibody are used for severe forms of the disease (1). The European League Against Rheumatism (EULAR) announced an evidence-based BD management guideline (2018 edition) (34). Unfortunately, even in this guideline, no strong recommendation was made for special-type BD because of the limited amount of evidence. Azathioprine, cyclosporine A, interferon (not covered by insurance in Japan), and anti-TNF- α antibody are recommended for uveitis (35, 36). The use of anti-TNF- α antibody is recommended for special-type BD in addition to immunosuppressants. Guidelines for the management of BD are currently being developed by the Japan BD Research Committee.

The Japanese government has approved the anti-TNF- α antibodies infliximab (IFX) and adalimumab for the treatment BD. In BD, combination with methotrexate (MTX) is not required for IFX administration as in RA, but it is possible that production of human antibody against chimeric antibody may be suppressed by using concomitant immunosup-

Table 2. Loci Identified by GWASs and Similar Genetic Analyses of Behçet's Disease.

Year	Reference	Population	Loci
2009	69	Turkey	*
2010	26	Japan	<i>HLA-A*26 IL10 IL23R</i>
2010	28	Turkey	<i>HLA-A*03 IL10 IL23R</i>
2012	70	China	<i>STAT4</i>
2013	27	Turkey, Japan	<i>CCR1 STAT4 KLRC4 ERAP1</i>
2013	56	Turkey	<i>MEFV M694V</i>
2013	71	Korea	*
2014	72	Iran	<i>FUT2</i>
2015	73	European, Middle East	<i>IL12A</i>
2017	29	Turkey, Japan, Iran	<i>IL1B, IRF8, IL12A, FUT2, RIPK2, EGR2, LACC1, PTPN1</i>

Loci with genome-wide evidence ($p < 5.0 \times 10^{-8}$) are listed in the table.

*No loci with genome-wide significance were identified. IL: interleukin, FUT2: fucosyltransferase 2, HLA: human leukocyte antigen, STAT: signal transducer and activator of transcription, KLRC: killer cell lectin-like receptor subfamily C, member 4, ERAP: Endoplasmic reticulum aminopeptidase 1, MEFV: Mediterranean Fever, IRF8: interferon regulatory factor 8 binding protein, RIPK2: receptor interacting serine/threonine kinase 2, EGR2: early growth response 2, LACC1: laccase domain containing 1, PTPN1: protein tyrosine phosphatase, non-receptor type 1

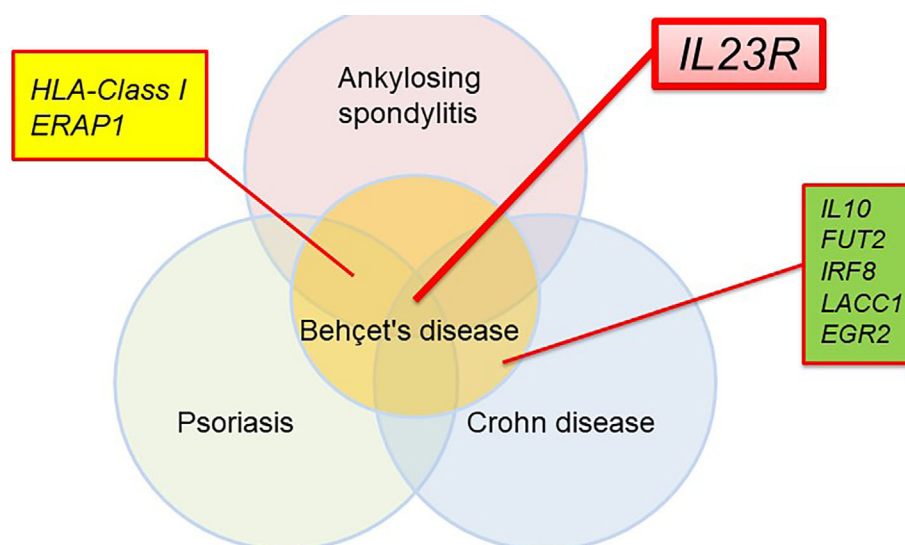


Figure 2. Overlapping genetic architecture of Behçet's disease, ankylosing spondylitis, psoriasis, and Crohn's disease. The *IL23R* gene lies in the center of the circles. HLA-Class I and *ERAP1* are both found in BD, AS, and psoriasis.

pressants, such as MTX and AZA (37). Anti-TNF- α antibody treatment for special-type BD is also covered by insurance in Japan. However, there is a lack of substantial evidence to support the use of anti-TNF- α antibody for these rare conditions; only a small study with an open-label single-arm clinical trial has examined this approach (38, 39). In addition, the efficacy of the phosphodiesterase 4 inhibitor apremilast reached the primary endpoint in a phase 2 double-blind, randomized controlled trial of BD stomatitis (40). Apremilast has insurance indications for psoriasis in Japan (41).

At present, several biologics that manipulate IL-17 pathways, such as antibodies against IL-12/IL-23, and IL-17A,

can be used to treat psoriasis in Japan (42). As described above, *IL23R* is a susceptible gene for BD and psoriasis; these anti-Th17 treatments strategy may therefore be of benefit for BD (43). The Janus kinase (Jak)-STAT pathway inhibitor is indicated for RA (44). As *STAT4* is a susceptibility gene for both RA and BD, Jak inhibitor may be useful for the treatment of BD (27, 45).

Pathogenesis of BD from Genetic and Environmental Aspects

Finally, we summarize the possible mechanisms proposed based on GWASs and epidemiological analyses of BD.

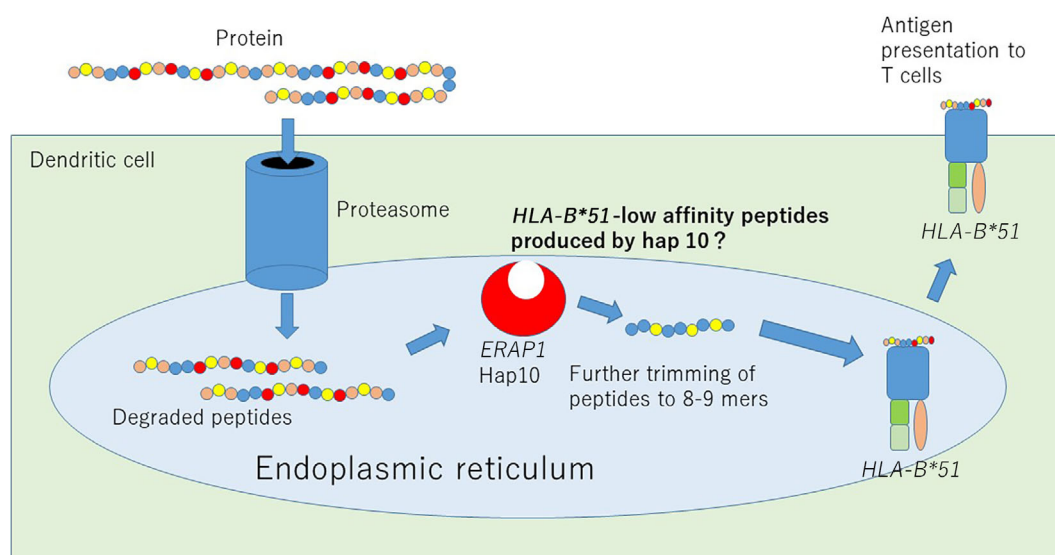


Figure 3. *ERAP1*-mediated antigen processing in BD. Proteins engulfed by dendritic cells (DC) are first degraded by proteasomes. Through TAP, peptides enter the endoplasmic reticulum (ER) and are further trimmed by *ERAP1*. *ERAP1* hap10, the low-activity form of *ERAP1*, produces *HLA-B*51*-low-affinity peptides. These peptides bind to HLA within the ER and then move to the surface of the DC, where they are eventually recognized by T cells.

i) Pathway involved in peptide binding to HLA

In AS, psoriasis, and BD, gene interaction is found between single nucleotide polymorphism (SNP)s of HLA-Class I and *ERAP1* (27, 46-48), which is a rare phenomenon showing an effect more than the additive effect between two independent genes and is genetic evidence that genes exhibiting interaction functionally cooperate with each other to contribute to the pathological condition. In BD, AS, and psoriasis, the process by which a specific peptide to a particular HLA-Class I antigen is presented via *ERAP1* is vital for disease pathogenesis (Fig. 3). Indeed, it was recently reported that *ERAP1* allotype 10 (a type containing R725Q polymorphism, also called hap10), which is a risk factor for BD, is likely to produce *HLA-B*51* low-affinity peptides (49). Because homozygosity but not heterozygosity of *ERAP1* hap10 carries a substantial risk for BD (48), we suggest that a deficiency in BD-protective peptides, which may “put a lid on” *HLA-B*51*, produced by *ERAP1* hap10 activates *HLA-B*51*-mediated inflammation in BD.

ii) Natural killer cells

KLRC4, another BD-susceptible locus, encodes NKG2F, a natural killer (NK) receptor whose function is largely unknown (50). The role of the similar gene NKG2D has been studied intensively in the field of transplantation (51, 52). NKG2D recognizes MICA, a gene that resides next to HLA-B. GWASs have revealed that *HLA-B*51* and MICA-allele A6 are in strong linkage disequilibrium, suggesting that MICA might play an additional role to *HLA-B*51* in BD (53, 54). As a result, MICA expressed on the surface of the target cells may be recognized by the NK receptor NKG2F, thereby potentially inducing NK cell-dependent cell

cytotoxicity to the target cells. As mentioned above, the production of BD-protective peptides might be reduced by *ERAP1* hap10, which further decreases *HLA-B*51*-bound peptides, resulting in lower HLA-B expression at the cell surface. NK cells may attack such “*HLA-B*51*^{low}-MICA^{high}” mucocutaneous cells via NK receptor NKG2F. In addition, the NK receptors killer immunoglobulin-like receptor (KIR) KIR3DL1, which inhibits the NK function, and KIR3DS1, which activates the NK function, recognize *HLA-B*51* Bw4 motif (55). A recent study evaluated the presence of KIR3DL1 or KIR3DS1 alleles in Turkish BD patients bearing HLA-B with a Bw4 motif. However, there no significant differences in the presence between BD patients and controls (55). Further functional studies are needed to clarify whether or not an abnormality in the balance of these two receptors has functional consequence in BD.

iii) Th17 cells

As mentioned above, the IL-23 receptor (*IL23R*) is associated with SpA (Fig. 2). The disease-protective variant *IL23R* R381Q is associated with reduced IL-23 dependent IL-17 production (56). IL23R mediates Th17 T cell differentiation and is a susceptibility gene not only for SpA but also for bacterial infection leprosy (57). It is likely that the immune response of Th17 cells to bacteria is involved in BD.

iii) Autoinflammation

Genetic evidence for an innate immune response in BD comes from a candidate gene analysis performed by next-generation sequencing. We reported that mutations in the innate immune receptors *TLR4* and *NOD2* are associated with BD (56). Furthermore, Turkish *MEFV* M694V, a causative variant of familial Mediterranean fever (FMF), is associated

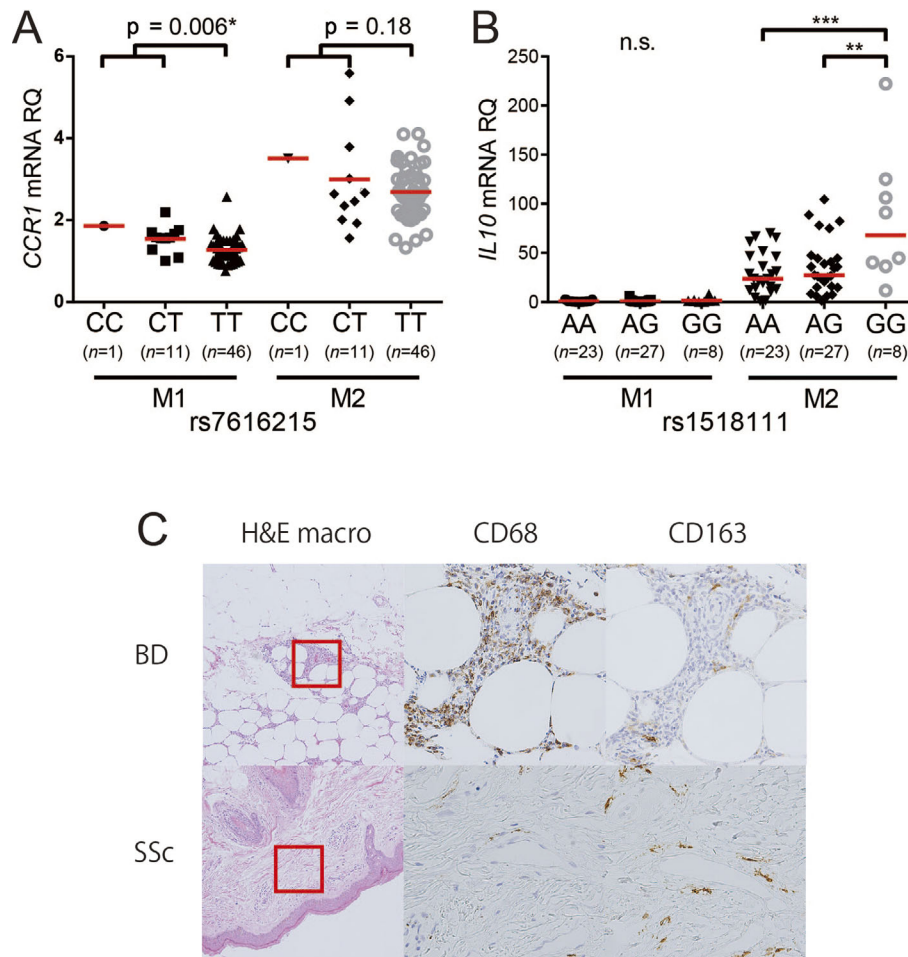


Figure 4. The relationship between SNP genotypes associated with Behçet's disease and the *CCR1* and IL-10 expression by M1 and M2 macrophages. **A:** The *CCR1* mRNA expression of M1 and M2 macrophages and genotypes of SNP rs7616215 (the T allele carries a risk of Behçet's disease), **B:** The IL-10 mRNA expression of M1 and M2 macrophages and genotypes of SNP rs1518111 in *IL10* (the A allele carries a risk of Behçet's disease), **C:** Hematoxylin and Eosin staining in BD nodular erythema, differences in the expression of the pan-macrophage marker CD68 and the M2 macrophage marker CD163 (modified from Nakano et al.⁶⁴).

with BD (56). *MEFV* M694V is not prevalent in Japanese, but the allele frequency of the similarly FMF-causative mutation M694I was found to be 0.1-0.3% in the Japanese population. *MEFV* encodes the protein pyrin, which detects structural changes in Rho GTPase induced by toxins, such as that of *Clostridium difficile*, leading to IL-1 β production by pyrin-inflammasome formation (58). Macrophages from individuals with *MEFV* exon 10 mutations (M694I, M694V, etc.) spontaneously produce IL-1 β due to constitutive pyrin-inflammasome activation (59). Furthermore, our recent genetic analysis identified SNPs associated with IL-1 β production in BD (29). The BD-susceptible locus *FUT2* is thought to be essential for controlling intestinal bacterial flora and is also associated with IBD (29).

Overall, genetic evidence suggests that intestinal bacteria are involved in the development of BD. Indeed, a microbiome analysis suggests dysbiosis in BD patients (60). Control of the immune response against microorganisms is a potential treatment strategy for BD that should be considered

in the future.

iv) Polarized macrophages

One limitation of GWASs is that they do not tell us the operational basis of the locus, necessitating further basic research. Expression quantity locus (eQTL) analyses have been performed in the context of GWASs (61). A BD GWAS showed that loci *IL10* and *CCR1* are highly expressed in the monocyte/macrophage lineage (27, 28). IL-10 is an anti-inflammatory cytokine, and its deficiency causes infantile-onset severe IBD mimicking BD (62). Indeed, SNPs with a lower IL-10 expression are associated with a risk of BD (28). *CCR1* is a chemokine receptor involved in cell migration. Surprisingly, a lower rate of monocyte migration was identified as a risk factor for BD (27). Macrophages have a subset of inflammatory M1 and anti-inflammatory M2 (63). Human peripheral blood monocytes that differentiate to M2 *in vitro* with macrophage colony stimulating factor (M-CSF) stimulation exert anti-inflamma-

tory effects through the production of IL-10. We found that the BD disease susceptibility polymorphisms of *CCR1* and *IL10* loci affect the expression of these gene products in M1/M2 macrophages, leading to M1-predominant inflammation in BD (Fig. 4). We postulate that a decreased *CCR1*-dependent M2 macrophage migration through GWAS-identified SNPs may therefore result in augmented inflammation due to decreased IL-10 supplementation and SNP-dependent decreased IL-10 production (64).

vi) *NFκB* signaling

Recently, a whole-exome analysis of familial BD identified a heterozygous germline mutation in *TNFAIP3* encoding A20, a regulatory protein suppressing the *NFκB* signaling pathway (65). Patients with the A20 mutation exhibit constitutive *NFκB* activation in their leukocytes. A genetic analysis of the Mendelian form of BD would facilitate our understanding of the disease pathogenesis.

vii) Environmental factors

The phenotypic evolution of Japanese BD patients over the last 20 years may be related to environmental changes, as the genetic admixture in the Japanese population has been small over the past thousand years. The mechanisms underlying the increased intestinal BD in Japan may be similar to those underlying the increased incidence of Crohn's disease, which has been attributed to the increased dietary intake of n-6 polyunsaturated fatty acids and animal protein in Japanese (66). Such nutritional changes in Japan may be altering the gut microbiome, resulting in an increased prevalence of IBD (67, 68). A lower *HLA-B*51* positivity in intestinal BD than in complete-type BD suggests that intestinal BD is a genetically distinct population (3). Although the specific environmental factors affecting the prevalence of BD are still unknown, each BD phenotype is presumably affected by different environmental factors.

Conclusion

We summarized the recent clinical and basic findings in BD. Both environmental factors and a genetic predisposition are essential for the onset of BD. Enacting measures against environmental factors, even after the onset of the disease, such as maintaining a clean oral cavity, treating periodontal disease, and stopping smoking, are important. For severe organ inflammation, early intervention with effective therapies, such as anti-TNF- α antibody, may ameliorate the cumulative organ damage caused by the disease. The identification of the characteristics and prognosis of distinct BD phenotype groups, such as intestinal BD, through national registration is necessary. Clinical trials with domestic and overseas collaboration will be important for establishing robust evidence-based therapies and disease cluster-specific therapies targeting BD.

The authors state that they have no Conflict of Interest (COI).

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